

(19)



Europäisches Patentamt  
European Patent Office  
Office européen des brevets



(11) **EP 1 050 301 A1**

(12)

**EUROPEAN PATENT APPLICATION**

published in accordance with Art. 158(3) EPC

(43) Date of publication:  
08.11.2000 Bulletin 2000/45

(21) Application number: 99900351.0

(22) Date of filing: 19.01.1999

(51) Int. Cl.<sup>7</sup>: **A61K 31/135**, A61K 47/40,  
A61K 47/26, A61K 9/08

(86) International application number:  
PCT/JP99/00152

(87) International publication number:  
WO 99/36065 (22.07.1999 Gazette 1999/29)

(84) Designated Contracting States:  
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU  
MC NL PT SE  
Designated Extension States:  
AL LT LV MK RO SI

(30) Priority: 19.01.1998 JP 804598

(71) Applicant:  
YOSHITOMI PHARMACEUTICAL INDUSTRIES,  
LTD.  
Osaka-shi Osaka 541-0046 (JP)

(72) Inventors:  
• SAKAI, Atsushi,  
Yoshitomi Pharma. Industries Ltd.  
Chikujo-gun, Fukuoka 871-8550 (JP)

- MASUDA, Rumiko,  
Yoshitomi Pharma. Industries Ltd.  
Chikujo-gun, Fukuoka 871-8550 (JP)
- FUJII, Tsuneo,  
Yoshitomi Pharma. Industries, Ltd.  
Chikujo-gun, Fukuoka 871-8550 (JP)
- MISHINA, Tadashi,  
Yoshitomi Pharma. Ind. Ltd.  
Iruma-shi, Saitama 358-0026 (JP)
- CHIBA, Kenji,  
Yoshitomi Pharma. Industries, Ltd.  
Iruma-shi, Saitama 358-0026 (JP)

(74) Representative:  
von Kreisler, Alek, Dipl.-Chem. et al  
Patentanwälte,  
von Kreisler-Selting-Werner,  
Bahnhofsvorplatz 1 (Deichmannhaus)  
50667 Köln (DE)

(54) **MEDICINAL COMPOSITIONS**

(57) The present invention provides a pharmaceutical composition containing 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable acid addition salt thereof, and cyclodextrin as a stabilizer, and where necessary, saccharide, which can be prepared into a liquid agent, and which is useful for the suppression of rejection in organ or bone marrow transplantation, immunosuppressive sustention therapy therefor or the treatment of autoimmune diseases.

EP 1 050 301 A1

**Description****Technical Field**

5 **[0001]** The present invention relates to a pharmaceutical composition containing 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable acid addition salt thereof as an active ingredient and to a composition for a kit. More particularly, the present invention relates to a pharmaceutical composition containing 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable acid addition salt thereof and cyclodextrin as a stabilizer, which is suitable for the suppression of rejection in organ (e.g., kidney, liver, heart, small bowel  
10 etc.) or bone marrow transplantation, immunosuppressive sustention therapy therefor and the treatment of autoimmune diseases, and which can be formulated into a liquid agent.

**Background Art**

15 **[0002]** 2-Amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol and a pharmaceutically acceptable acid addition salt thereof are known to be useful as suppressants of rejection in organ or bone marrow transplantation and as therapeutic agents for various autoimmune diseases, such as psoriasis, Behçet's disease and the like, and rheumatic diseases, as described in WO94/08943.

**[0003]** While this compound has been developed as a preparation for oral administration, when it is used as a suppressant of rejection in organ or bone marrow transplantation, the administration thereof immediately after transplantation is desired for the quickest possible exertion of the effect. In view of the condition of patient, however, since oral administration is difficult for the patient, it is administered by injection. When this compound is used for diseases of the eye, such as Behçet's disease, moreover, it needs to be applied as an eye drop.

**[0004]** The above-mentioned WO94/08943 describes a preparation of this compound as an injection, and discloses the use of polyethylene glycol and ethanol as solubilizers. However, polyethylene glycol shows undesirable effects such as local irritation and hemolysis and its use is problematic. Ethanol is neither suitable for an injection because it causes local irritation.

**[0005]** WO97/24112 discloses, as an external agent of this compound, an eye drop containing this compound and, as a solubilizer, hydrogenated polyoxyethylene castor oil, which is a surfactant.

30 **[0006]** When the above-mentioned compound, particularly 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride (hereinafter to be also referred to as the present compound throughout the specification), is dissolved in distilled water, the problems occur that the aqueous solution shows hemolytic property, foams due to the surface-activating property that the compound itself has, and shows precipitation of the present compound in the aqueous solution as crystals at a certain concentration due to the dissolution mechanism peculiar to the present compound, despite the fact that the present compound is water-soluble. In addition, an aqueous solution of the present compound incorporating an isotonicity agent (e.g., sodium chloride etc.) and/or a solubilizer (e.g., hydrogenated polyoxyethylene castor oil etc.) or a tackifier (e.g., polyvinylpyrrolidone etc.) as additives, that are generally used for liquid agents such as injection and eye drop, is associated with the above-mentioned problems of hemolysis, foaming and crystal precipitation, and none of the above are satisfactory.

40 **[0007]** JP-A-7-316065 discloses an FR901469 preparation containing cyclodextrin, which shows decreased hemolytic property and less local irritation, and JP-A-7-228532 discloses an aqueous liquid agent containing cyclodextrin, which shows enhanced water solubility and enhanced stability in water of a hardly water soluble agent. JP-A-133960/1976 discloses a method of eliminating foams produced by a surfactant for industrial use, which comprises adding cyclodextrin to a foamed aqueous solution containing the surfactant.

**Disclosure of the Invention**

50 **[0008]** In view of the above situation, the present inventors have conducted intensive studies in an attempt to obtain a pharmaceutical composition containing 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable acid addition salt thereof, which is associated with less side effects, such as hemolysis, or local irritation, which is superior in defoaming performance, and which can be formulated into a liquid agent, such as an injection and an eye drop, that is free from crystal precipitation of the active ingredient compound, and found that the incorporation of cyclodextrin can achieve such object, which resulted in the completion of the present invention.

55 **[0009]** Accordingly, the present invention provides a pharmaceutical composition containing 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable acid addition salt thereof and cyclodextrin, which can be readily prepared into a pharmaceutical agent, which is associated with less side effects, such as hemolysis, or local irritation, which is superior in defoaming performance, and which is suitable for a liquid agent free from crystal precipitation of the active ingredient compound. The present invention characteristically resolves all the aforementioned prob-

lems simultaneously by the incorporation of cyclodextrin as a stabilizer along with 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable acid addition salt thereof, and is particularly characterized in that it provides a liquid agent superior in defoaming performance and free from crystal precipitation of the active ingredient compound. In the present invention, it has been also found that the incorporation of a saccharide selected from monosaccharides, disaccharides and sugar alcohols results in a liquid composition further improved in local irritation.

[0010] The pharmaceutical composition of the present invention contains 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable acid addition salt thereof as an active ingredient and cyclodextrin as a stabilizer, and where desired, a saccharide.

[0011] The present invention also provides use of cyclodextrin for the preparation of a pharmaceutical composition containing cyclodextrin, wherein crystal precipitation of the active ingredient compound has been inhibited, an inhibitor of crystal precipitation of the active ingredient compound in a pharmaceutical composition containing cyclodextrin, and a medical agent wherein crystal precipitation of the active ingredient compound in a pharmaceutical composition has been inhibited.

[0012] The 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol and a pharmaceutically acceptable acid addition salt thereof, that are the active ingredients of the pharmaceutical composition of the present invention, can be produced according to the method described in WO94/08943. Preferred compound is 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride. As other acid addition salts, there are exemplified hydrobromide, sulfate, acetate, fumarate, maleate, benzoate, citrate, malate, methanesulfonate, benzenesulfonate and the like.

[0013] The 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable acid addition salt thereof is added in a proportion of 0.01 - 20 wt%, particularly preferably 0.1 - 10 wt%, of the total weight of the composition.

[0014] The cyclodextrin to be used in the present invention is naturally occurring cyclodextrin, branched cyclodextrin, alkyl cyclodextrin or hydroxyalkyl cyclodextrin. Specifically exemplified are  $\alpha$ -cyclodextrin (e.g., trademark: Cerdex A-100 manufactured by Nihon Shokuhin Kako Co., Ltd.),  $\beta$ -cyclodextrin (e.g., trademark: Cerdex B-100 manufactured by Nihon Shokuhin Kako Co., Ltd.),  $\gamma$ -cyclodextrin (e.g., trademark: Cerdex G-100 manufactured by Nihon Shokuhin Kako Co., Ltd.), dodecakis-2,6-O-methyl- $\alpha$ -cyclodextrin, tetradecakis-2,6-O-methyl- $\beta$ -cyclodextrin, hexadecakis-2,6-O-methyl- $\gamma$ -cyclodextrin, tetradecakis-2,6-O-ethyl- $\beta$ -cyclodextrin,  $\alpha$ -cyclodextrin partially etherified with 2-hydroxypropyl,  $\beta$ -cyclodextrin partially etherified with 2-hydroxypropyl (HP- $\beta$ -CyD, e.g., trademark: Cerdex HP- $\beta$ -CD manufactured by Nihon Shokuhin Kako Co., Ltd.), branched  $\alpha$ -cyclodextrin and branched  $\beta$ -cyclodextrin wherein glucose and maltose have been bonded via  $\alpha$ -1,6-glucoside bond, and the like. These cyclodextrins are added in an amount of 1-50 parts by weight, particularly preferably 10-30 parts by weight, per part by weight of the above-mentioned active ingredient.

[0015] The saccharide to be used in the present invention is selected from monosaccharides, disaccharides and sugar alcohols, and is exemplified by glucose, fructose, D-maltose, lactose, sucrose, D-mannitol, D-xylitol and D-sorbitol, which may be used alone or in combination. These saccharides are added in an amount of 1-100 parts by weight, particularly preferably 5-80 parts by weight, per part by weight of 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable acid addition salt thereof.

[0016] When 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable acid addition salt thereof (particularly hydrochloride) is prepared into an aqueous solution, it foams at a concentration of 0.01 - 20 wt%, and causes hemolysis and local irritation. The present compound shows special dissolution mechanism wherein, when it is prepared into an aqueous solution having a concentration higher than 0.1 wt%, it is dissolved after forming micelle, and at a concentration lower than 0.05 wt%, it is dissolved to give a solution without forming micelle. As a result of this unique dissolution mechanism, crystals are precipitated in an aqueous solution having a concentration of 0.05 - 0.1 wt%. The incorporation of cyclodextrin into the aqueous solution enables inhibition of the precipitation of crystals due to the formation of micelle, as well as simultaneous resolution of the problems of foaming, hemolysis and local irritation, which characterizes the present invention.

[0017] The pharmaceutical composition of the present invention takes the preparation form of a liquid agent, which may be injection, eye drop, nose drop, ear drop, infusion, liquid for oral administration, liquid for inhalation, liquid for lotion and the like, with preference given to injection (intravenous, subcutaneous, intramuscular, etc.) eye drop and infusion. These preparation forms are appropriately selected according to the diseases to be treated, conditions thereof, sex and age of patient, application site and the like, and the preparation is formulated by a method known to those of ordinary skill in the art.

[0018] The pharmaceutical composition of the present invention can be placed in the market as a completed liquid preparation, or as a kit including a powder or lyophilized product containing the active ingredient etc. and a liquid for dissolution. For example, the active ingredient, 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable acid addition salt thereof (particularly hydrochloride) is dissolved in purified water and the resulting solution is sterilized by filtration, filled in vials and freeze-dried in vacuo to give lyophilized products. As a liquid for dissolution, an aqueous solution is prepared by dissolving cyclodextrin to be used in the present invention and, where nec-

essary, saccharide, in distilled water. The aforementioned lyophilized product can be dissolved in the liquid for dissolution when in use. The liquid for dissolution is used in a 5-fold to 2000-fold amount (parts by weight) relative to the amount of 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable acid addition salt thereof. As used herein, the distilled water is preferably distilled water for injection in the case of an injection. The aforementioned lyophilized product is generally filled in vials, and after displacement with nitrogen, applied with a rubber stopper and sealed with aluminum, after which the product can be stored for a long time at room temperature. The cyclodextrin and saccharide to be further added where necessary can be contained in the lyophilized product together with the active ingredient, 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable acid addition salt thereof, rather than in the liquid for dissolution as mentioned above. The cyclodextrin is added in an amount of 1 - 50 parts by weight, particularly preferably 10 - 30 parts by weight, per part by weight of the above-mentioned active ingredient. The saccharide to be further added where necessary is added in an amount of 1 - 100 parts by weight, particularly preferably 5 - 80 parts by weight, per part by weight of the above-mentioned active ingredient.

[0019] The pharmaceutical composition of the present invention may appropriately contain, besides the above-mentioned ingredients, solubilizer, isotonicity agent, pH adjusting agent, buffer, antioxidant, thickener, surfactant, preservative, humectant, aromatic, coloring agent and the like. These additives may be added when formulating the pharmaceutical composition of the present invention into a preparation or may be added to the liquid for dissolution in the kit preparation for dissolution when in use.

[0020] The pharmaceutical composition of the present invention can be used for the suppression of rejection after organ or bone marrow transplantation, immunosuppressive sustention therapy therefor or the treatment of the diseases of the eye such as Behçet's disease, uveitis and the like, dermatitis inclusive of psoriasis, atopic dermatitis, contact dermatitis and allergic dermatitis, and the like. More particularly, the pharmaceutical preparation of the present invention can be used for the prophylaxis and treatment of various applicable symptoms conventionally performed with oral preparations, such as for immunosuppression in organ or bone marrow transplantation, various autoimmune diseases, various allergic diseases and the like.

[0021] Accordingly, the composition of the present invention can be used as a liquid agent for the prophylaxis and treatment of resistance or rejection in organ or tissue transplantation (e.g., transplantation inclusive of allograft of heart, kidney, liver, lung, bone marrow, cornea, pancreas, small bowel, limb, muscle, nerve, fatty marrow, duodenum, skin, pancreatic islet cell etc.), graft-versus-host (GvH) disease in bone marrow or small bowel transplantation, autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, nephrotic syndrome lupus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes mellitus, type II adult onset diabetes mellitus, uveitis, nephrotic syndrome, steroid-dependent and steroid-resistant nephrosis, palmoplantar pustulosis, allergic encephalomyelitis, glomerulonephritis etc.), and infectious diseases caused by pathogenic microorganisms. The composition of the present invention can be also used for the treatment of the onset of inflammatory, proliferative and ultraproductive skin diseases and immunologically-mediated diseases of the skin, such as psoriasis, psoriatic arthritis, atopic eczema (atopic dermatitis), contact dermatitis and further, eczematous dermatitis, seborrheic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythema, cutaneous eosinophilias, acne, alopecia areata, eosinophilic fasciitis and atherosclerosis. The pharmaceutical composition of the present invention can be more particularly used for hair revitalizing, such as in the treatment of female or male pattern alopecia or senile alopecia by providing epilation prevention, hair germination and/or promotion of hair generation and hair growth.

[0022] The composition of the present invention can be also used for the treatment of respiratory diseases such as sarcoidosis, pulmonary fibrosis, idiopathic interstitial pneumonia and reversible obstructive airways disease including conditions such as asthma including bronchial asthma, infantile asthma, allergic asthma, intrinsic asthma, extrinsic asthma and dust asthma, particularly chronic or inveterate asthma (e.g., late asthma and airway hyperresponsiveness), and bronchitis and the like. The composition of the present invention can be also used for liver disorders associated with ischemia. Moreover, it is effective for specific eye disease such as conjunctivitis, keratoconjunctivitis, keratitis, vernal conjunctivitis, uveitis associated with Behçet's disease, herpetic keratitis, conical cornea, dystopia epithelialis corneae, keratoleukemia, ocular pemphigus, Mooren's ulcer, scleritis, Graves' ophthalmopathy, severe intraocular inflammation and the like.

[0023] The composition of the present invention can be also used for the prophylaxis and treatment of inflammation of mucosa or blood vessels such as leukotriene B<sub>4</sub>-mediated diseases, gastric ulcer, damage of blood vessel due to ischemic diseases and thrombosis, inflammatory bowel diseases (e.g., Crohn's disease and ulcerative colitis) and necrotizing enterocolitis, and intestinal lesions associated with thermal burns. The inventive composition can be used for the prophylaxis and treatment of renal diseases such as interstitial nephritis, Goodpasture's syndrome, hemolytic uremic syndrome and diabetic nephropathy; neuropathy selected from multiple myositis, Guillain-Barre syndrome, Meniere's disease and radiculopathy; endocrine diseases such as hyperthyroidism and Basedow's disease; hematologic diseases such as pure red cell aplasia, aplastic anemia, hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis and anerythroplasia; bone diseases such as osteoporosis; respiratory

diseases such as sarcoidosis, pulmonary fibrosis and idiopathic interstitial pneumonia; skin disease such as dermatomyositis, vitiligo vulgaris, ichthyosis vulgaris, photoallergic sensitivity and cutaneous T cell lymphoma; circulatory diseases such as arteriosclerosis, aortitis, polyarteritis nodosa and amyocardosis; collagen diseases such as scleroderma, Wegener's granulomatosis and Sjögren's syndrome; adiposis; eosinophilic fasciitis; periodontal disease; nephrotic syndrome; hemolytic uremic syndrome; and muscular dystrophy.

[0024] The inventive composition is also suitable for the prophylaxis and treatment of inflammation/allergy of intestine, such as Coeliac disease, proctitis, eosinophilic gastroenteritis, mastocytosis, Crohn's disease, ulcerative colitis; and allergic diseases associated with food, which shows symptoms directly irrelevant to gastrointestinal tract, such as migraine, rhinitis and eczema.

[0025] 2-Amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol and a pharmaceutically acceptable acid addition salt thereof, which are the active ingredients of the pharmaceutical composition of the present invention, have liver regenerating activity and/or activity of promoting hypertrophy and hyperplasia of hepatocytes. Therefore, the inventive composition can be used for the prophylaxis and treatment of liver diseases such as immunogenic diseases (e.g., chronic autoimmune liver diseases including autoimmune hepatitis, primary biliary cirrhosis and sclerosing cholangitis), partial hepatectomy, acute liver necrosis (e.g., necrosis caused by toxins, viral hepatitis, shock or anoxia), B-virus hepatitis, non-A/non-B hepatitis and cirrhosis.

[0026] The composition of the present invention can be also used as a composition for antibacterial agent, and therefore, can be used for the treatment of the diseases caused by pathogenic microorganisms. Moreover, the inventive composition can be used for the prophylaxis and treatment of malignant rheumatoid arthritis, amyloidosis, fulminant hepatitis, Shy-Drager syndrome, pustular psoriasis, Behçet's disease, systemic lupus erythematosus, endocrine ophthalmopathy, progressive systemic sclerosis, mixed connective tissue disease, aortitis syndrome, Wegener's granulomatosis, active chronic hepatitis, Evans syndrome, pollinosis, idiopathic hypoparathyroidism, Addison disease (autoimmune adrenalitis), autoimmune orchitis, autoimmune oophoritis, cold hemagglutinin disease, paroxysmal cold hemoglobinuria, pernicious anemia, adult T cell leukemia, autoimmune atrophic gastritis, lupoid hepatitis, tubulointerstitial nephritis, membranous nephritis, amyotrophic lateral sclerosis, rheumatic fever, postmyocardial infarction syndrome and sympathetic ophthalmitis.

[0027] Where the case demands, the composition of the present invention can be used concurrently with other immunosuppressant(s), steroid(s) (e.g., prednisolone, methyl prednisolone, dexamethasone, hydrocortisone etc.) or nonsteroidal anti inflammatory agents. Particularly preferable other immunosuppressants is selected from azathioprine, brequinar sodium, deoxyspergualin, mizoribine, mycophenolic acid 2-morpholinoethyl ester, cyclosporine, rapamycin, tacrolimus monohydrate, leflunomide and OKT-3.

[0028] Though subject to change depending on the disease to be treated, conditions thereof, sex and age of patient, application site and the like, the composition of the present invention containing the active ingredient of the present compound and the like in a proportion of 0.00001 - 20 wt%, preferably 0.0001 - 10 wt%, can be applied one to several times (e.g., 2-5 times) a day to achieve a clinically preferable effect.

#### Best Mode to Practice the Invention

[0029] The present invention is explained in more detail in the following by referring to Examples, Comparative Examples and Experimental Examples.

[0030] In the following examples, any proportion is based on weight and shows w/v%, unless otherwise specified. In the examples, the present compound means 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride, as mentioned above.

#### Example 1

[0031] An injection containing the present compound, which has the following formulation, is produced.

present compound	0.1%
$\alpha$ -cyclodextrin (trademark: Cerdex A-100)	1.0%
D-mannitol	5.0%

[0032] The above composition is dissolved in distilled water for injection to give an injection having the total amount of 10 ml. Where necessary, typical additives, such as preservative, can be incorporated.

**Example 2**

[0033] An injection containing the present compound, which has the following formulation, is produced.

present compound	0.1%
$\beta$ -cyclodextrin partially etherified with 2-hydroxypropyl (trademark: Cerdex HP- $\beta$ -CD)	1.0%
D-mannitol	5.0%

[0034] The above composition is dissolved in distilled water for injection to give an injection having the total amount of 10 ml. Where necessary, typical additives, such as preservative, can be incorporated.

**Example 3**

[0035] An injection containing the present compound, which has the following formulation, is produced.

present compound	0.1%
$\alpha$ -cyclodextrin (trademark: Cerdex A-100)	1.0%

[0036] The above composition is dissolved in distilled water for injection containing typical additives, such as preservative, where necessary. After sterilization by filtration, the total amount of 10 ml is packed in a vial, which is lyophilized by a conventional method to give an injection.

**Example 4**

[0037] An injection containing the present compound, which has the following formulation, is produced.

present compound	0.1%
$\beta$ -cyclodextrin partially etherified with 2-hydroxypropyl (trademark: Cerdex HP- $\beta$ -CD)	1.0%

[0038] The above composition is dissolved in distilled water for injection containing typical additives, such as preservative, where necessary. After sterilization by filtration, the total amount of 10 ml is packed in a vial, which is lyophilized by a conventional method to give an injection.

**Example 5**

[0039] An injection containing the present compound, which has the following formulation, is produced.

present compound	0.1%
$\beta$ -cyclodextrin partially etherified with 2-hydroxypropyl (trademark: Cerdex HP- $\beta$ -CD)	2.0%
sodium chloride	0.9%

[0040] The above composition is dissolved in distilled water for injection to give an injection having the total amount of 10 ml. Where necessary, typical additives, such as preservative, can be incorporated.

**Example 6**

[0041] An eye drop containing the present compound, which has the following formulation, is produced.

5

present compound	0.1%
$\alpha$ -cyclodextrin (trademark: Cerdex A-100)	1.0%
D-mannitol	5.0%

10

[0042] The above composition is dissolved in sterile purified water to give an eye drop having the total amount of 10 ml. Where necessary, typical additives, such as preservative, can be incorporated.

15

**Example 7**

[0043] An eye drop containing the present compound, which has the following formulation, is produced.

20

present compound	0.1%
$\beta$ -cyclodextrin partially etherified with 2-hydroxypropyl (trademark: Cerdex HP- $\beta$ -CD)	1.0%
D-mannitol	5.0%

25

[0044] The above composition is dissolved in sterile purified water to give an eye drop having the total amount of 10 ml. Where necessary, typical additives, such as preservative, can be incorporated.

30

**Comparative Example 1**

[0045]

35

present compound	0.1%
------------------	------

[0046] The present compound is dissolved in distilled water for injection to give an injection having the total amount of 10 ml.

**Comparative Example 2**

[0047]

45

present compound	0.1%
sodium chloride	0.9%

50

[0048] The above composition is dissolved in distilled water for injection to give an injection having the total amount of 10 ml.

55

# EP 1 050 301 A1

## Comparative Example 3

[0049]

5

present compound	0.1%
D-mannitol	5.0%

10

[0050] The above composition is dissolved in distilled water for injection to give an injection having the total amount of 10 ml.

## Comparative Example 4

15

[0051]

20

present compound	0.1%
D-mannitol	5.0%
sodium laurylsulfate	1.0%

25

[0052] The above composition is dissolved in distilled water for injection to give an injection having the total amount of 10 ml.

## Comparative Example 5

30

[0053]

35

present compound	0.1%
D-mannitol	5.0%
polysorbate 80	1.0%

40

[0054] The above composition is dissolved in distilled water for injection to give an injection having the total amount of 10 ml.

## Comparative Example 6

45

[0055]

50

present compound	0.1%
D-mannitol	5.0%
hydrogenated polyoxyethylene castor oil 60 (HCO-60)	1.0%

55

[0056] The above composition is dissolved in distilled water for injection to give an injection having the total amount of 10 ml.



## Comparative Example 7

[0057]

5

present compound	0.1%
D-mannitol	5.0%
polyvinylpyrrolidone 12 PF	1.0%

10

[0058] The above composition is dissolved in distilled water for injection to give an injection having the total amount of 10 ml.

15

## Experimental Example 1: Hemolysis test

[0059] The preparations obtained in Examples 1 and 2 were prepared into sample solutions according to "Yakuan No. 2" (Test method for topical disorder caused by injection (draft), January 12, 1979, Safety Section, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare) and the absorbance at 540 nm was measured according to the method of Inglot et al., Biochem. Pharmacol. Vol. 17, p. 269 (1968). As a result, the preparations of Examples 1 and 2 were found to have significantly lower hemolytic property. In contrast, the preparations of comparative Examples 1-7 showed hemolytic property.

20

## 25 Experimental Example 2: Local Irritation test

[0060] The preparation obtained in Example 1 was intravenously repeat administered to 5-week-old LEW rats for 5 consecutive days and local irritation was confirmed using swelling ratio of the tail {diameter of tail of drug administration group - diameter of tail of control} ÷ diameter of tail of control × 100} as an index. As a result, the preparation of Example 1 achieved 0%, showing presence of no local irritation.

30

## Experimental Example 3: Crystal precipitation test

[0061] The preparations obtained in Examples 1 and 2 were sterilized by filtration, filled in ampoules, melt-sealed and sterilized by heating at 121°C for 20 minutes to give injections having the total amount of 2 ml. These preparations were left standing at room temperature for 1 week. As a result, the preparations of Examples 1 and 2 showed no precipitation of crystals. The preparations of Examples 1 and 2 were left standing in a refrigerator for 1 week. Neither preparation showed precipitation of crystals. In contrast, the preparations of Comparative Examples 1, 2, 3, 4 and 7 showed precipitation of crystals both at room temperature and in cold storage.

35

40

## Experimental Example 4: Foaming test

[0062] The ampoules were stood erected, laid down and then stood erected, which steps were taken as one cycle. This cycle was repeated 10 times for the preparations obtained in Examples 1 and 2. The generated foams disappeared within 1 minute in the case of the preparations obtained in Examples 1 and 2, demonstrating a remarkably short defoaming time. In contrast, the generated foams did not disappear for at least 5 minutes in the case of the preparations of Comparative Examples 1-7.

45

## Industrial Applicability

50

[0063] A pharmaceutical composition containing 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable acid addition salt thereof, which is suitable for a liquid agent, which can be readily prepared into a pharmaceutical agent, which shows less side effects, such as hemolysis, less local irritation and superior defoaming performance, and which inhibits crystal precipitation of the active ingredient compound, can be provided by the addition of cyclodextrin as a stabilizer to 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable acid addition salt thereof. Incorporation of saccharide into this composition results in an even more reduced local irritation.

55

[0064] This application is based on application No. 8045/1998 filed in Japan, the contents of which are incorporated

hereinto by reference.

# Claims

- 5 1. A pharmaceutical composition comprising 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable acid addition salt thereof as an active ingredient, and cyclodextrin as a stabilizer.
2. The pharmaceutical composition of claim 1, wherein the cyclodextrin is naturally occurring cyclodextrin, branched cyclodextrin, alkyl cyclodextrin or hydroxyalkyl cyclodextrin.
- 10 3. The pharmaceutical composition of claim 1, wherein the cyclodextrin is incorporated in an amount of 1 - 50 parts by weight per part by weight of 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable acid addition salt thereof.
- 15 4. The pharmaceutical composition of claim 1, further comprising saccharide.
5. The pharmaceutical composition of claim 4, wherein the saccharide is selected from monosaccharides, disaccharides and sugar alcohol.
- 20 6. The pharmaceutical composition of claim 4 or claim 5, wherein the saccharide is one or more kinds selected from D-mannitol, glucose, D-xylitol, D-maltose, D-sorbitol, lactose, fructose and sucrose.
7. The pharmaceutical composition of claim 4, wherein the saccharide is contained in an amount of 1 - 100 parts by weight per part by weight of 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable acid addition salt thereof.
- 25 8. The pharmaceutical composition of claim 1, wherein the active ingredient is inhibited from precipitating out as crystals.
- 30 9. The pharmaceutical composition of claim 1 or claim 8, wherein the active ingredient is contained in a proportion of 0.05 - 0.1 wt% of the composition and the cyclodextrin is contained in a proportion of 1 - 50 parts by weight per part by weight of the active ingredient.
- 35 10. A pharmaceutical composition comprising cyclodextrin, wherein crystal precipitation of an active ingredient compound in the composition is inhibited.
11. An inhibitor of crystal precipitation of an active ingredient compound in a pharmaceutical composition comprising cyclodextrin.
- 40 12. The inhibitor of claim 11, wherein the active ingredient compound is in the form of an aqueous solution.
13. The pharmaceutical composition of claim 1, which is superior in defoaming property, shows reduced hemolytic property, and which causes less local irritation.
- 45 14. A composition for a kit comprising a lyophilized product of 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable acid addition salt thereof, and a liquid for dissolution comprising an aqueous solution containing cyclodextrin.
- 50 15. A composition for a kit comprising a lyophilized product comprising 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable acid addition salt thereof and cyclodextrin, and a liquid for dissolution comprising distilled water.
16. The composition of claim 14 or claim 15, wherein the cyclodextrin is contained in an amount of 1 - 50 parts by weight per part by weight of 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable acid addition salt thereof.
- 55 17. The composition of claim 14 or claim 15, wherein one or both of the lyophilized product and the liquid for dissolution comprise(s) saccharide.

18. The composition of claim 17, wherein the saccharide is contained in an amount of 1 - 100 parts by weight per part by weight of 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable acid addition salt thereof.

5

10

15

20

25

30

35

40

45

50

55

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP99/00152

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>		
Int.Cl. <sup>6</sup> A61K31/135, A61K47/40, A61K47/26, A61K9/08		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b>		
Minimum documentation searched (classification system followed by classification symbols)		
Int.Cl. <sup>6</sup> A61K31/135, A61K47/40, A61K47/26, A61K9/08		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
CAPLUS (STN), MEDLINE (STN)		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO, 96/06068, A1 (YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD.), 29 February, 1996 (29. 02. 96), Full text & EP, 778263, A1	1-9, 12-18
A	WO, 94/08943, A1 (YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD.), 28 April, 1994 (28. 04. 94), Full text & EP, 627406, A1 & US, 5604229, A	1-9, 12-18
A	JP, 7-316065, A (Fujisawa Pharmaceutical Co., Ltd.), 5 December, 1995 (05. 12. 95), Particularly abstract (Family: none)	1-9, 12-18
A	JP, 58-148816, A (Nippon Zenyaku Kogyo K.K.), 5 September, 1983 (05. 09. 83), Particularly page 1, left column (Family: none)	1-9, 12-18
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 5 April, 1999 (05. 04. 99)		Date of mailing of the international search report 11 May, 1999 (11. 05. 99)
Name and mailing address of the ISA/ Japanese Patent Office		Authorized officer
Facsimile No.		Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP99/00152

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP, 5-213757, A (Senju Pharmaceutical Co., Ltd.), 24 August, 1993 (24. 08. 93), Particularly abstract & EP, 472327, A1	1-9, 12-18
A	JP, 6-16547, A (Wakamoto Pharmaceutical Co., Ltd.), 25 January, 1994 (25. 01. 94), Particularly abstract (Family: none)	1-9, 12-18
A	JP, 7-228532, A (Senju Pharmaceutical Co., Ltd.), 29 August, 1995 (29. 08. 95), Particularly abstract & EP, 621036, A1 & US, 5605892, A	1-9, 12-18
A	JP, 8-175985, A (Lion Corp.), 9 July, 1996 (09. 07. 96), Particularly abstract (Family: none)	1-9, 12-18
P, X	WO, 98/03162, A1 (YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD.), 29 January, 1998 (29. 01. 98), Full text (Family: none)	1-9, 12-18
X	EP, 335545, A2 (UNIVERSITY OF FLORIDA), 27 August, 1989 (27. 08. 89) & JP, 2-9825, A & US, 4983586, A & US, 5017566, A & US, 5024998, A	10, 11
X	JP, 63-253022, A (Nitto Denko Corp.), 20 October, 1988 (20. 10. 88) (Family: none)	10, 11

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP99/00152

**Box I** Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II** Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

The group of inventions as set forth in claims 1 to 9 and 12 to 18 aims at using 2-amino-2-(2-(4-octylphenyl)ethyl)propane-1,3-diol or pharmaceutically acceptable acid-addition salts thereof as the essential active ingredient and not only suppressing crystallization thereof but also relieving foaming and the inherent hemolytic nature and local pungency of the compound by using together cyclodextrins as stabilizers. In contrast, the groups of inventions as set forth in claims 10 and 11 aims at preventing crystallization of indefinite active compounds by adding cyclodextrins.

Such being the case, the group of inventions as set forth in claims 1 to 9 and 12 to 18 and the group of inventions as set forth in claims 10 and 11

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.